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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,991	05/10/2001	Andreas Gerardus Uitterlinden	KILS117128	1133

26389 7590 04/19/2002

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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	7

DATE MAILED: 04/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/786,991	Applicant(s) UITTERLINDEN ET AL.	
	Examiner Sally Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6,7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Specification/Informalities

1. The disclosure is objected to because of the following informalities:

A. It is unclear whether Tables 1-4 intend to be part of the specification or if these tables are considered to be figures. If the tables are intended to be part of the specification, then the figures should be inserted into the specification, prior to the claims. The sheet labeled "FIG. 1" should also be amended to delete the recitation of "5/5". If the tables are intended to be figures, then the tables should be re-labeled as Figures 2, 3, 4, and 5 and a brief description of these figures should be added to the specification.

B. The specification at pages 13-14 refers to Tables 3a, 3b, 4a, and 4b. However, the application contains only tables labeled 3 and 4 (i.e., the application does not contain a Table 3a, 3b, 4a or 4b).

C. The specification is objected to because it does not contain, as a separate section, a brief description of the drawings, as required by 37 CFR 1.74. Page 12, line 17 of the specification should be amended to include the title "BRIEF DESCRIPTION OF THE DRAWINGS".

D. The specification is objected to because there are discrepancies concerning the restriction enzyme sites within the VDR gene. The specification includes *BsmI, ApoI,* and *TaqI* as the three sites of interest within the VDR gene. Claim 2 however reads *BsmI, ApaI,* and *TaqI* as the three restriction enzyme sites of interest within the VDR gene. This claim should be amended to recite "*ApoI*".

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22 and 23 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

3. Claims 3, 6-10, 19, 20, 23, 25-26, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and kits for diagnosing susceptibility to bone fracture comprising detecting the presence of the G to T polymorphism at the Sp1 site of the collagen Iα1 gene, in conjunction with detecting the baT haplotype of the vitamin D receptor gene, the specification does not provide enablement for methods and kits for determining the susceptibility to bone fracture comprising detecting any allele of the collagen Iα1 gene in conjunction with detecting the baT haplotype of the vitamin D receptor gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 3, 6-10, 19, 20, 23, 25, 26, and 29 are broadly drawn to methods and kits for diagnosing susceptibility to bone fracture comprising analyzing the genetic material of a subject to determine which allele of the collagen Iα1 gene is present. The specification teaches

susceptibility to bone fracture comprising the detection of the presence of the G to T polymorphism at the Sp1 site of the collagen Iα1 gene. The claims do not specify which allele, of the collagen Iα1 gene, in what copy number, is present in a subject to determine their susceptibility to bone fracture. Furthermore, the specification provides no guidance as to how to predictably identify additional alleles of the collagen Iα1 gene that are associated with bone damage. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate what allele in the collagen Iα1 gene may exist to cause a subject to be susceptible to bone fracture. The claims are drawn to a potentially very large genus of polymorphisms(i.e., any polymorphism or mutation in the collagen Iα1 gene), yet the specification teaches only one polymorphism in the collagen Iα1 gene associated with bone fracture(i.e., the G to T polymorphism at the Sp1 site). Therefore, the specification has not taught a representative number of species within the claimed genus. Furthermore, the specification does not provide sufficient guidance as to how to select additional alleles of the

collagen Iα1 gene associated with bone fracture because the specification does not teach, for example, how modifying the collagen Iα1 gene product results in bone fracture nor does it teach where mutations may occur in the collagen Iα1 gene product which would cause a change in the gene product's activity and would make an individual more susceptible to bone damage. Therefore additional alleles can only be identified by randomly analyzing the collagen Iα1 gene sequence and determining whether any of these alleles are correlated with bone fracture. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

4. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22 and 23 provide for the use of the kit for determining susceptibility to bone fracture, but, since the claim does not set forth any steps involved in the method, it is unclear what method the applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

B. Claims 1-6, 7-17,and 27-30 are indefinite for failing to recite a final process step which agree back with the preamble. The claims are drawn to a method of determining susceptibility to

bone fracture. However, the claims recite only a single step of determining the presence of a baT haplotype. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for determining the susceptibility of a subject to bone fracture or to methods for detecting a baT haplotype. The claims should be amended to clarify that detection of the baT haplotype is indicative of an increased susceptibility to bone fracture.

C. Claims 2-4, 6-10, 13-14, and 28-30 are indefinite because it is unclear as to how these claims are intended to be further limiting from claim 1. Claim 1 is drawn to a method of determining susceptibility to bone fracture. However, claim 2 recites a method of determining susceptibility to bone damage. Since bone damage is not equivalent to bone fracture, it is unclear as to whether claim 2 is intended to be limited to methods for determining susceptibility to bone fracture or to methods for determining susceptibility to bone damage.

D. Claim 13 is indefinite for failing to recite a final process step that agrees back with the preamble. Claim 13 depends from claim 1, which is limited to methods for determining susceptibility to bone fracture. However, claim 13 recites a final step of further treating the subject to reduce the risk of bone fracture. Accordingly, it is unclear as to whether claim 13 is intended to be limited to methods for determining the susceptibility of a subject to bone fracture or methods for treating a subject to reduce the risk of bone fracture.

E. Claims 18-21 are indefinite for failing to recite a final process step that agrees back with the preamble. Claim 18 is drawn to a method of predicting response of a subject to treatment. However, claim 18 recites a final step of detecting a baT haplotype. Accordingly, it is unclear as to whether claim 18 is intended to be limited to methods for predicting response of a subject to a treatment or for methods of detecting a baT haplotype.

F. Claim 20 is indefinite for failing to recite a final process that agrees back with the preamble. Claim 20 depends from claim 18 that is limited to methods of predicting response of a subject to treatment. However, claim 20 recites a final step of diagnosing susceptibility to bone fracture. Accordingly, it is unclear as to whether claim 20 is intended to be limited to methods of predicting the response of a subject to treatment or methods of diagnosing susceptibility to bone fracture.

G. Claim 21 is indefinite for failing to recite a final process that agrees back with the preamble. Claim 21 depends from claim 18 or 19 which are limited to methods of predicting response of a subject to treatment. However, claim 21 recites a final step of administering an appropriate treatment. Accordingly, it is unclear as to whether claim 21 is intended to be limited to methods of predicting the response of a subject to treatment or methods of administering an appropriate treatment.

H. Claims 24, 25, and 26 are indefinite over the recitation of "said allele(s)" because this phrase lacks proper antecedent basis. While the claims previously refer to a baT haplotype, the claims do not previously refer to alleles.

I. Claim 25 and 26 are indefinite over the recitation of "said gene" because this phrase lacks proper antecedent basis. While the claims previously refer to the vitamin D receptor gene and the collagen Iα1 gene the claim most recently refers to the vitamin D receptor gene as "said gene." The claim should be amended to clarify and provide adequate antecedent basis.

J. Claims 27-30 are indefinite. The terms "may be determined" and "relevant portion" in claim 27-30 are relative terms that render the claim indefinite. The terms "may be determined" and "relevant portion" are not defined by the claim, the specification does not provide a standard

for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims should be amended to clarify whether or not the haplotype "may be determined." Additionally, an amendment is necessary to clarify what the "relevant portion" of the vitamin D receptor gene really is.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

6. Claims 18, 21, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Spector et al. (U.S. Patent No. 5939260).

Spector et al. teaches a method for predicting the response of a subject to treatment wherein this method comprises analyzing the nucleic acid of the subject and detecting the presence of the baT haplotype of the vitamin D receptor gene. Spector teaches that individuals having the baT haplotype are more susceptible to osteoarthritis. Following the diagnosis of the subject's susceptibility to osteoporosis, a method of preventative or palliative therapy for osteoarthritis is provided before the disease becomes significantly established(column 1). Spector states that based on the diagnostic results, the "decision of a physician on how and whether to initiate therapy in anticipation of the disease can be taken with increased confidence"(column4). The reference also teaches a number of suitable treatments for patients diagnosed with susceptibility to or having osteoarthritis such as exercise to keep joints flexible,

surgery to prevent or control joint stress, and the use of pharmaceutical treatments that modify symptoms or disease agents are among the variety of therapies to which the reference alludes.

With respect to claim 24, Spector(column 5) teaches kits for determining the susceptibility to osteoarthritis of a subject comprising a "diagnostic composition" and an "indicator composition". The diagnostic composition may include PCR primers for amplifying the *TaqI, BsmI* and/or *ApoI* polymorphisms. The indicator composition includes the means for correlating the vitamin D receptor gene polymorphisms with predisposition to susceptibility to osteoarthritis. The reference teaches the use of a leaflet or other visual reminder as a suitable indicator(column 5).

Furthermore, as stated in MPEP 211.02, "When the claim is directed to a product, the preamble is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property in the old composition. *Kropa v. Robie,* 187 F.2d at 152, 88 USPQ at 480-481". The MPEP (2112) further states that the "claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable". Accordingly, the identification of a new use (i.e. of determining susceptibility to bone fracture) for the known kit comprising one or more primer molecules for amplification of a portion of the VDR, means for determining the haplotype present, and means for indicating a correlation between the haplotype present and the risk of bone fracture does not render the kit novel.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 19, 21, 25, and 26 are rejected under U.S.C. 103(a) as being unpatentable over Spector et al. (US patent 5939260) in view of Ralston.

Spector et al. teaches a method for predicting the response of a subject to treatment wherein this method comprises analyzing the nucleic acid of the subject and detecting the presence of the baT haplotype of the vitamin D receptor gene. Spector teaches that individuals having the baT haplotype are more susceptible to osteoarthritis. Following the diagnosis of the subject's susceptibility to osteoporosis, a method of preventative or palliative therapy for osteoarthritis is provided before the disease becomes significantly established(column 1). Spector states that based on the diagnostic results, the "decision of a physician on how and whether to initiate therapy in anticipation of the disease can be taken with increased confidence"(column4). The reference also teaches a number of suitable treatments for patients

diagnosed with susceptibility to or having osteoarthritis such as exercise to keep joints flexible, surgery to prevent or control joint stress, and the use of pharmaceutical treatments that modify symptoms or disease agents are among the variety of therapies to which the reference alludes.

Spector(column 5) also teaches kits for determining the susceptibility to osteoarthritis of a subject comprising a "diagnostic composition" and an "indicator composition". The diagnostic composition may include PCR primers for amplifying the *TaqI, BsmI* and/or *ApoI* polymorphisms. The indicator composition includes the means for correlating the vitamin D receptor gene polymorphisms with predisposition to susceptibility to osteoarthritis. The reference teaches the use of a leaflet or other visual reminder as a suitable indicator(column 5). Spector does not teach the detection of polymorphisms at a second locus, namely the collagen Iα1 gene. However, Ralston teaches that the G to T polymorphism in the collagen Iα1 gene is associated with risk of osteoporosis(abstract). The reference also teaches that those individuals diagnosed as being more susceptible to osteoporosis should be given preventative therapy before irreversible bone loss has occurred. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Spector so as to have included a step of further detecting the G to T Sp1 polymorphism in the collagen Iα1 gene in order to have provided an effective method which allowed for the simultaneous determination of an individual's risk of developing osteoarthritis and developing osteoporosis and of providing an accurate means for determining an individuals response to treatment for these conditions.

With respect to claims 25 and 26, it would have been further obvious to one of ordinary skill in the art to have included the primers for amplifying the Sp1 polymorphism and means for detecting amplification of the collagen Iα1 gene in the kit of Spector for the expected advantage

of generating a kit that allowed for the analysis of both the baT haplotype of the VDR gene and the Sp1 polymorphism of the collagen Iα1 gene for individuals in the art wishing to determine an individual's susceptibility to osteoarthritis and osteoporosis. Furthermore, with respect to claim 26, the combined references do not teach including a DNA control in the kit. However, a person of ordinary skill in the art would include the use of a DNA control. Therefore it would have been obvious to one skilled in the art at the time the invention was made to have included a DNA control in the kit of Spector for the expected benefit of generating a kit that provided a more accurate means of detecting the baT haplotype of the VDR gene although no specifically stated.

9. Claim 26 is rejected under U.S.C. 103(a) as being unpatentable over Spector et al. (US patent 5939260).

Spector et al teach a kit comprising nucleotide primer molecules for amplification of portions of the VDR gene in addition to a means for determining said haplotype and its subsequent correlation to a phenotype. Spector teaches the use of a control in their study's population with respect to a phenotypic trait of knee osteoarthritis grade 1(Column 7). Spector does not teach the use of a DNA control. However, a person of ordinary skill in the art would include the use of a DNA control. Therefore it would have been obvious to one skilled in the art at the time the invention was made to have included a DNA control in the kit of Spector for the expected benefit of generating a kit that provided a more accurate means of detecting the baT haplotype of the VDR gene although no specifically stated.

Conclusion

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantai Dessau whose telephone number is (703)605-1237.

SALLY SAKELARIS
4/15/02

CARLA J. MYERS
PRIMARY EXAMINER